REMARKS

I. Claim Rejections—35 U.S.C. § 112

Claims 66-78 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The Examiner states the term "smaller vessels" in claim 66 and "stable microbubbles" in claim 35, appear to be relative terms which render the claim indefinite. The Examiner states the term "smaller vessels" or "stable microbubbles" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. In effect, what is the point of reference or nature of comparison in determining the smaller vessels or stable microbubbles.

Applicant has amended claim 66 by deleting the relative term "smaller", thus alleviating this rejection.

Applicant traverses the rejection that "stable microbubbles" is a relative term.

The claims read in light of the specification reasonably apprise one skilled in the art both in utilization and scope of the invention. Absent a special or expressed definition, terms should be given their ordinary and accustomed meaning. Therefore, someone tutored in this relevant art would understand upon reading the claim that "stable microbubbles" means as disclosed in the specification on page 12, lines 18-20, that the microbubbles must be not be readily altering in their physical state. (See Merriam-Webster Dictionary on-line version at ~~www.m-w.com/cgi-bin/dictionary~~ for the defintion of "stable"). Moreover, the term stable is not relative because it is not being used in a comparison sense but to describe its physical state. Thus, "stable" is not a

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relative term and one of ordinary skill in the art would be apprised in the scope of the invention. Thus, Applicant respectfully requests the Examiner to withdraw this rejection.

II. Double Patenting

Claims 66-79 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 5,648,098; claims 1-24 of U.S. Patent 6,197,345; claims 1-17 of U.S. Patent 5,980,950. The Examiner states although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims appear to overlap in scope.

The Examiner further states that the instant case is directed to methods of relieving trauma associated with obstruction of smaller vessels distal to a thrombus site comprising the same process steps as those of patented claims. The instant claims differ from the patented claims by the intended use. However, the intended use of the patented claims is directed for treating thrombosis and thus alleviating the surrounding tissue trauma. Thus, it would have been obvious to one of ordinary skill in the art at the time of invention to practice the instant claims when in possession of the patented claims.

Pursuant to MPEP 804.02 (IV), to avoid paying multiple terminal disclaimer fees, a single terminal disclaimer may be filed, wherein all the conflicting double patenting refererences are disclaimed therein. Therefore, Applicant is herein submitting a Terminal Disclaimer, which disclaims any term of the patent issuing from this application, which would extend beyond the term of Patent Nos. 5,648,098, 6,197,345, and 5,980,950. Applicant respectfully request Examiner to withdraw this rejection.

III. Claim Rejections—35 U.S.C. § 102

Claims 67-72 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5, 695,460 to Siegel.

The Examiner states Siegel discloses methods for utilizing a combination of ultrasonic energy and an echo contrast agent containing microbubbles for dissolving blood clots or other vascular obstructions. Siegel specifically discloses the use of echo contrast agents containing dodecafluoropentane and sonicated albumin (see column 2, lines 48-57). Siegel further discloses the use of a thrombolytic agent in combination to the contrast agents mentioned above (see column 3, lines 14-40, column 9-14, claims 1, 10, 15). Finally, Siegel discloses the use of Albunex as the suitable sonicated albumin. Albunex contains microbubbles having average diameter size within 2-10 micron. Therefore, Siegel anticipates limitations of the instant claims.

Applicant has amended claim 67 to include a limitation not expressly or inherently described in U.S. Patent No. 5,695,460 to Siegel. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 678, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Siegel fails to describe the limitation of the concentration of a carrier as indicated by the Examiner on page 5 of the Office Action, therefore, Siegel does not anticipate the limitations of the instant claims. Applicants respectfully request Examiner to withdraw this rejection.

IV. Claim Rejections—35 U.S.C. § 103

Claims 66-78 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Siegel in view of Feinstein U.S. Patent No. 4,572,203, Cerny et al. U.S. Patent No. 4,957,656, and Schutt, U.S. Patent No. 5,605,673.

The Examiner states that Siegel fails to specifically disclose the optimal concentrations for the albumin and the carrier.

Feinstein and Cerny collectively set forth various suitable concentrations and methodologies for employing albumin and a dextrose carrier system. Feinstein and Cerny teach methods of formulating Albunex echo contrast agent or similar type of protein-shelled, gaseous microspheres in the field of ultrasound imaging. (See Feinstein, column 2, lines 46-68, column 8, lines 1-46, claims 1, 18-19; and Cerny, column 8, and claims 1, 2, 4-5). Feinstein and Cerny also acknowledge the use of their contrast agents in treating blood flow abnormalities (see Feinstein, column 8, lines 1-10; Cerny incorporates the teachings of Feinstein in his patent). However, Feinstein and Cerny do not employ perfluorinated gases in their microbubble containing contrast agents in treating thrombus associated blood flow abnormalities.

Schutt provides for the use of various types of perfluorinated gases such as perfluorobutane and perfluoropropane in protein-shelled gaseous microbubbles in ultrasound contrast agents. (See abstract, column 16, lines 1-30). Schutt also suggest the use of his perfluorocarbon containing microbubbles in enhancing coronary flow with thrombolytic agents (column 11, lines 28-33).

Accordingly, the Examiner states it would have been obvious to one of ordinary skill in the art at the time of the invention to optimize the concentrations of albumin and dextrose in Siegel's formulations as suggested in Feinstein and Cerny by routine experimentation, and further substitute the decafluorpentane of Siegel with other perfluorocarbons such as perfluorbutane or perfluoropropane, because as shown by Schutt, such moeities are considered to be art equivalent, and absence of showing unexpected results, they are expected to provide similar therapeutic results.

Applicant traverses this rejection. There is no suggestion in the references that they be combined in the manner suggested by the Examiner. Absent such a suggestion, a person skilled in the art who is looking for a solution to the problem of to removing a thrombosis using echo contrast agents containing microbubbles utilized in conjunction with ultrasound as exhibited by Siegel would hardly be disposed on any objective basis to consider the reference like Feinstein, Cerny, and Schutt. Feinstein and Cerny are not only unconcerned with employing perfluorinated gases in microbubbles, but shows absolutely no recognition of employing such perfluroinated gases in microbubbles containing contrast agents in treating thrombosis associated blood flow abnormalities, as stated by the Examiner in the Office Action on November 20, 2002, page 6, lines 2-4.

Schutt merely teaches a method for forming microbubbles which relies on the use of combinations of gases to harness or cause differentials and partial pressures and to generate gas osmotic pressures, which stabilize the bubbles (see column 14, lines 64-67). There is no suggestion in Schutt that it be combined in the manner suggested by the Examiner. Absent such a suggestion, a person skilled in the art who is looking to a solution to a method of removing a thrombosis using echo contrast agents containing microbubbles utilized in combination with ultrasound like Siegel would hardly be disposed on any objective basis to consider a reference like Schutt which is unconcerned with echo contrast agents utilized in conjunction with ultrasound. Thus, claim 66-78 are patentable over Siegel in view of Feinstein, Cerny, and Schutt. Applicant respectfully request Examiner to withdraw this rejection.

No fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Reconsideration and allowance is respectfully requested.

Respectfully submitted,

Heidi S. Nebel, Reg. No. 37,719
McKEE, VOORHEES & SEASE, P.L.C.
801 Grand Avenue, Suite 3200
Des Moines, Iowa 50309-2721
Phone No. (515) 288-3667
Fax No. (515) 288-1338
CUSTOMER NO: 27140

Attorneys of Record

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AMENDMENT — VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims

Please cancel claim 70.

Please amend claim 66 as follows:

66. (Amended)

A method of relieving trauma associated with obstruction of [smaller] vessels distal to a thrombus site by increasing blood flow with or without thrombus dissolution and recanalization in animals comprising:

introducing a pharmaceutical composition to an animal with a thrombus by intravenous injection,

said pharmaceutical composition comprising a microbubble ultrasound agent, and a pharmaceutically acceptable carrier, wherein said carrier comprises a 5% solution of dextrose and thereafter;

applying ultrasound to the area of trauma.